A REVIEW ON ASSOCIATION OF ANEMIA WITH CHRONIC HEART FAILURE IN ELDERS

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OBJECTIVES

Primary aim of the study was to find association of anemia with chronic heart failure in elders.

ABSTRACT

Anemia is a condition that develops when a person's red blood cell count or hemoglobin level is less than the normal range. It is a problem mostly associated with people having congestive heart failure and is more widely recognized as a serious and treatable illness. The majority of the patients having congestive heart failure tend to be females who have hardly any heart disease or the associated risk factors, but have increased rates of diseases other than cardiovascular disorders and diastolic failures. The two most influential risk factors for congestive heart failure are hypertension & diabetes, especially in those females having coronary heart failure. Hospitalization of patients over the age of 65 is largely concerned with congestive heart failure, and it has a significant clinical and financial impact. Co-occurring, poly-pharmacy, as well as impairments related to congestive heart failure, account for around half of all hospital readmissions. Furthermore, congestive heart failure comes at a high price due to poor prognosis, having an average 1-year mortality rate of 33% to35%. Even though more than half of congestive heart failure patients fall under the category of 75 years, still certain trials have included younger patients having an average age of 61 years. It is concluded that anemia is prevalent as co-morbid condition. Furthermore, iron deficiency was identified as common reason for anemia in heart failure patients.

KEYWORDS: *Cardiac Heart Failure, Hypertension, Anemia*

How to cite this article
Umair M, Ahmad S, Majid A, Ullah N. A Review on Association of Anemia with Chronic Heart Failure in Elders. J Wazir Muhammad Inst Paramed Tech. 2022;2(2): 52-58

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INTRODUCTION

Among the patients with heart diseases, anemia is a common condition and it becomes more common as heart failure increases, renal function deteriorates, and people get older. In all patient populations, anemia is consistently linked to a worse rate of survival. Anemia is a strong determinant of death and a reason of hospitalization in most of the patients with systolic and diastolic failures, and also new occurrences of severe and chronic heart failure.[1,2] The frequency, pathogenesis, as well as pathophysiologic effects of anemia in patients having CHF are discussed in this review. It also discusses recent findings related to the effects of anemia on clinical outcomes, impacts of anemia treatment, as well as the non-hematopoietic outcomes of erythropoietin (EPO).[2] Congestive heart failure (CHF) has become a major public health concern with epidemic proportions. Present therapy options primarily focus on inhibiting pathologically overactive neurohormonal pathways. Despite the development of medications that predominantly produce neurohormonal blocking, the incidence and fatality related to chronic heart failure remains unacceptable,

implying that this treatment option has reached the limit. As a result, identifying the risk factors responsible for the poor results of the present therapy, as well as developing novel treatment options and preventive approachesare critical for improving the management of CHF.[3] Almost half of all the patients of CHF anemic (having Hb level less than 12 grams per deciliter). As the severity of CHF worsens, it in turns worsens the prevalence as well as severity of anemia. The effect of anemia on the heart of healthy people is less severe as compared to those patients with coronary heart disease. Ischemic heart disease can occur at highhemoglobin (Hb) level in persons with a damaged heart than in those with a healthy heart.[4]

CHF AND ANEMIA PREVALENCE

About 4%- 61% of patients with CHF (median 18 percent) are affected by anemia.[5] WHO defines anemia as the Hb level of 13gdL in males and 12gdL in postmenopausal females. On the other hand, the National Kidney Foundation defines anemia as aHb level of 12 gdL in both males as well as postmenopausal females. These 2 definitions, as well as some other study-related definitions, have been used in a variety of publications that explains the variations reported in the prevalence of anemia. This is reported in the analysis of data from the SOLVD (Studies of Left Ventricular Dysfunction) trial, performed by Al-Ahmad and colleagues.[6] Anemia had a prevalence rate of 22 percent when defined as a hematocrit of 39 percent (about a 13 gdLHb concentration); yet, it was only 4 percent when defined as a hematocrit of 35 percent (roughly a 12 gdLHb concentration).[7] This discrepancy emphasizes the urgent need for a unified definition of medically important anemia in heart failure patients. Secondly, the diverse clinical characteristics of the patient populations studied can be attributable to the large variability of anemia prevalence reported in patients of CHF. According to the NYHA (New York Heart Association) patients with functional class IV heart failure refractory to medical treatment are more likely to be anemic with an estimated frequency of 80 percent. Whereas, in patients of NYHA functional class I or II the prevalence observed was 10%.[6,8] Furthermore, the severity of CHF increases the severity of anemia. Silverberg and colleagues found that mean Hb dropped from 13.6 gdL to 10.9 gdL in NYHA functional class I and class IV respectively. Moreover, research showed that increased CHF severity was related to decreased Hb level, with mean Hb level declining from 14.1 gdL to 13.6 gdL in NYHA functional class II and class IV respectively.[9]

EPIDEMIOLOGY OF CHF

In Western countries, the prevalence and incidence of CHF are rising, especially among people over the age of 80 years.[10] According to Framingham data, one in five people would acquire CHF in their lifetime, and the risk increases with age, rising from 1.4%-1.9% among patients of middle age to 12.8%- 14.7% among octogenarians (80 -89 years).[11] Patients with advanced CHF were more likely to be female (almost 50% vs 35%; P 0.0001) with fewer heart illnesses and the associated risk factors, but had greater rates of diseases other than cardiovascular disorders.[12] Framingham Heart study showed that 80% of men and 70% of women belonging to the age of 65 with heart failure would die within 8 years.[13] Men have a lower survival rate after being diagnosed with CHF than women, whereas <15% of women survive for >8 to 12 years. One-year mortality is high, with 1 out of every 5 people dying. Shocking cardiac death occurs six to nine times more often in people with heart failure as compared to the general population.[13]

ETIOLOGY OF ANEMIA IN CHF

Few studies have thoroughly studied the causes responsible for anemia in individuals with CHF despite its increased frequency as well as the need of controlling the responsible mechanisms with effective therapy. Its etiology is complex in general. Four types of anemia play a crucial role in patients with CHF: chronic illness anemia, iron-deficiency anemia, renal anemia, as well as dilution anemia. All the present research indicates that in patients with CHF, chronic disease anemia plays a crucial role.[7,14,15]

IRON AND OTHER HEMATINIC DEFICIENCIES

The major cause of anemia in CHF patients appears to be hematinic deficiency.[5,16,17] This has been linked to decreased iron, folic acid, poor nutrition, malabsorption, cardiac cachexia as well as vitamin B12.[16] Defective iron release from cells can cause deficiency.[18] Furthermore, aspirin and oral anticoagulants can cause microscopic blood loss in the gastrointestinal tract, resulting in anemia. However, determining the iron level of CHF patients is difficult. The concentration of certain markers like; ferritin and transferrin (acute phase proteins) are changed in inflammatory

disorders.[19] In the measurement of 47 patients bone marrow aspirates the iron deficient anemic patients was 34(73%), and 3(5.4%) patients were dilution anemic, the drug-induced anemic patients was 2(2.5%), but for 9 patients no specific cause was identified (18.9% considered to have anemia of chronic disease.[4]

RENAL INSUFFICIENCY

The major contributor to anemia in people with CHF is chronic kidney failure. Low to high severity kidney disease, defined as glomerular filtration rate (GFR) of <60 mL/min in the absence of CHF, is concerned with lowered EPO synthesis as well as a gradual drop in Hb concentration that is directly in line with the decrease in GFR.[16] An estimated 25%–50% of CHF patients have a glomerular filtration rate of 60 mL/min.[15] Silverberg and his colleagues coined the term "cardio-renal anemia syndrome" which refer to a condition in which persistent CHF leads to renal failure, which in turn leads to anemia. Finally, impaired renal function and perfusion in individuals with chronic heart failure have been thought to be responsible for anemia.[20]

FUNCTION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Angiotensin II enhances the propagation of normal early elytroid progenitors by lowering nephritic blood circulation as well as boosting proximal tubular reabsorption, which increases EPO output.[21] The renin-angiotensin-aldosterone system is inhibited by the use of ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers which lowers EPO synthesis and Hb levels.[22] Furthermore, in the anemic patients with CHF the concentrations of the hematopoiesis inhibitor like; Acetyl-N-Ser-Asp-Lys-Pro (AcSDKP), which is virtually destroyed by ACE, are significantly higher. It may explain the anemia seen in ACE inhibitors treated patients.[23]

ROLES OF INFLAMMATION AND CHRONIC DISEASES

Inflammatory diseases are usually associated with lower Hb concentrations. Increased levels of pro-inflammatory cytokines or other inflammatory blood indicators, like C-reactive protein, are reciprocally associated with Hb levels in CHF patients.[24] Serum concentrations of pro-inflammatory cytokines also have a role in the development of anemia via various mechanisms. Serum necrosis factor-a, IL-1, and IL-6 disturb several mechanisms of erythropoiesis by lowering the nephritic secretion of EPO, repressing EPO activity in bone marrow, as well as by lowering the bioavailability of iron stores for the synthesis of Hb.[2] In HF increased plasma volume (hem dilution) can also lead to anemia, which is caused by the retention of salt and water. In anemic patients having severe CHF, An-drone and his colleagues found a 46 percent frequency of hem dilution.[25] Furthermore, hem dilution was found to be related to decrease Hb values in individuals with CHF in a recent study.[20]

PATHOPHYSIOLOGIC CONSEQUENCES OF ANEMIA

Decreased ejection fraction, as well as contractility, is the common manifestations of CHF in the elderly. Age-related myocardial and vascular wall stiffness and an increase in aortic resistance because increased end-diastolic pressure in a stiff ventricle that results in pulmonary congestion.[15,26] In the elderly heart, conditions like atrial fibrillation (highly common in such people) that further impede ventricular filling, have the potential to quickly precipitate heart failure decompensating.[26] In the absence of any underlying cardiac disease, severe chronic anemia (hematocrit level between 9% and 16%) can lead to heart failure.[4] Vasodilation is caused by tissue hypoxia, which is caused by a severe drop in Hb content. The sympathetic nervous system as a result is engaged, inducing tachycardia along with nephritic vasoconstriction, and as a result, systemic blood pressure drops. This activates the renin-angiotensin-aldosterone system which in turn leads to a reduction in nephritic blood circulation as well as GFR. These factors i.e.; activation of renin-angiotensin-aldosterone plus the reduction in GFR, manifest as central and peripheral inflammation as well as heart enlargement. Long-term dilation of the heart chambers, in combination with the renin-angiotensin-aldosterone and sympathetic nervous system hyperactivity, results in cardiac restructuring and CHF. In people with underlyingCHF, lesser degrees of anemia may be required for further worsening by activating neurohormonal pathways.[27] Anemia's impact on cardiac remodeling has been examined in the lab. It causes eccentric hypertrophy and enhanced capillary proliferation in rats, as well as a 50% increase in heart mass.[28] In individuals with renal illness, the connection between anemia and cardiac remodeling has also been intensively explored.

With the increase in LV mass index, a decrease in Hb concentration was observed by Levin and colleagues in the patients with the early nephritic disease while Foley and his colleagues noticed a decrease in Hb level that is linked with the rise in LV mass index in patients of chronic nephritic failure.[29,30] The development of new or repeated heart failure in the presence of LV distends was both associated with an increase in average Hb concentration. Furthermore, a 1-gdL increase in Hb level was related to a 4.1 gm 2 decrease in LV mass in a subgroup of patients involved in the trial of Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (Golden age).[9] However, no link was discovered between increased Hb concentration and decreased Hb concentration in some chronic renal disease patients treated with EPO drugs in LV hypertrophy.[31]

ANEMIA AND CHF DIAGNOSIS AND CLINICAL OUTCOMES

Anemia is a strong determinant of death and a reason for hospitalizations in patients with systolic and diastolic failures, the new occurrence of CHF as well as severe and chronic heart failure, according to a vast number of studies.[1,2] A 1-gdL drop in Hb level was independently related to the increased risk of mortality in analyses assessing Hb as a continuous variable. According to Harwich and colleagues, each 1-gdL reduction in Hb level raised the probability of death by 13% in individuals with advanced CHF. Similarly, Mozaffarian and colleagues researched patients with chronic heart failure, each 1% reduction in hematocrit level was associated with an 11% increased death risk in patients with a 37.5% baseline hematocrit.[2,3] Anemia was linked to lowered exercise capacity,[16,17,32] and an increased NYHA functional class,[5,8,15] shorter distance covered during 6-min walk tests, reduced peak oxygen utilization during cardiopulmonary exercise, decreased nephritic function, the more rapid development of renal disease, and adverse hemodynamic function in patients presenting with systolic cardiac failure. Anemia is associated high death rate, an increased likelihood of hospital stay, increased cerebral perfusion serum level, lower exercise capacity, and longer hospitalizations in diastolic failure patients.[7,17] 70% of CHF patients, including the one having diastolic failures, were lymphopenic, indicating extensive hematopoiesis disturbance in some individuals, possibly due to bone marrow suppression by higher cytokine concentrations.[33]

MANAGEMENT OF ANEMIA AND CHF

The link between anemia & the negative outcomes resulted in the concept that the treatment of anemia could improve the prognosis of CHF patients. Supplementation with hematinics, like; iron, and subcutaneous medicines which increase erythropoiesis are two specific therapies that has been studied.[13] EPO stimulates the bone marrow to increase the production of erythrocytes as well as to boost the survival and proliferation of erythroid precursor cells. The kidney is responsible for its production in response to hypoxia. Darbepoetinalfa (DA), a newer counterpart of EPO, has two extra N-linked carbohydrate sites, allowing it to lengthen its serum half-life by three times enabling the dose intervals to be extended more easily. The key findings from various investigations suggest the use of drugs that stimulate erythropoiesis like recombinant human EPO or hematinics such as iron, in the treatment of anemia in CHF. Small sample sizes and inadequate designs limit this research, which implies that treating anemia may reduce morbidity inCHF patients.[7] However, it would be unclear if increasing Hb anemia in CHF improves long-term prognosis as well as what sort of benefit this intervention may have on rates of hospital stay, quality of life, the capacity of exercise as well as mortality until larger, confirmatory, randomized studies are completed. Meanwhile, it's unclear if anemia therapy would benefit primarily highly symptomatic or severely anemic patients versus the general population. Treatment thresholds, target Hb, doses and durations of therapies, as well as the best way to raise Hb erythropoiesis-stimulating agents. As previously mentioned, anemic CHF patients typically have either relative or total iron insufficiency. Iron is required for erythropoiesis as well as various enzyme-dependent bio-energetic activities in skeletal muscle and the TCA cycle. Severe deficiency of iron can diminish exercise capacity and affect the ultrastructure of cardiac myocytes on its own. In anemic or non-anemic heart failure, iron-deficient patients, IV iron alone may be useful.[2,11, 32]

TREATMENT OF CHF

DIGOXIN

Digoxin is a medicine used for various heart problems like irregular heartbeats. It may be taken orally or intravenously. In NYHA class III or IV patients with atrial fibrillation and heart failure with severe systolic failure, digoxin is used as an inotropic drug. In this way, the function and quality

of life might increase but do not affect survival.[34]

ACE INHIBITORS

Angiotensin-converting-enzyme inhibitors or ACE are the categories of medicine recommended for treating elevated blood pressure as well as CHF. Their function is to allow the relaxation of the arteries as a result of which the volume of the blood drops. This results in the lowering of blood pressure as well as lower oxygen requirement from the heart.[34,35]

BETA-BLOCKERS

These are the specific drugs that are used for treating irregular heartbeats as well as for protecting the heart from a second heart attack. Besides this, these drugs can also be used for treating hypertension (high blood pressure), albeit they are no more the first-line treatment option for this condition.[3]

SPIRONOLACTONE

A drug used to treat fluid build-up in the body because of CHF, hepatic damage, or renal illness. It can also treat elevated BP and low potassium levels that don't respond to supplementation. Spironolactone is used to treat diseases like hyperaldosteronism and is also used in patients with edema caused due to renal and hepatic diseases.[32,34,35]

CONCLUSION

Among the people with CHF, anemia is present as a prevalent co-morbid condition and it's linked with poor long-term results. Iron deficiency appears to be the most common reason for anemia in heart failure patients. Furthermore, among CHF patients, anemia is a strong independent determinant of higher death rates as well as hospitalizations. Many studies have shown that treatment of anemia with supplementary hematinics, subcutaneous drugs that stimulates erythropoiesis, or a combination of both improves anemia prognosis in individuals with CHF. Anemia and chronic renal illness are commonly prevalent, where one promotes the other condition which is known as "cardio-renal anemia syndrome". Though anemia origin in heart failure is unknown evidence suggest that the activation of neurohormonal along with proinflammatory cytokine in heart failure favors the occurrence of chronic anemia illness.

CONFLICT OF INTEREST: None

FUNDING SOURCES: None

REFERENCES

1. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). Journal of the American College of Cardiology. 2003;41(11):1933-9.
2. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. Journal of the American College of Cardiology. 2002;39(11):1780-6.
3. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. American heart journal. 2006;151(2):457-62.
4. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. European Journal of Heart Failure. 2002;4(6):681-6.
5. Tang Y-D, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation. 2006;113(20):2454-61.
6. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. Journal of the American College of Cardiology. 2001;38(4):955-62.
7. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation. 2006;113(7):986-94.
8. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive

heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. Journal of the American College of Cardiology. 2000;35(7):1737-44.
9. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110(2):149-54.
10. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. The American journal of medicine. 2011;124(2):136-43.
11. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106(24):3068-72.
12. Stein GY, Kremer A, Shochat T, Bental T, Korenfeld R, Abramson E, et al. The diversity of heart failure in a hospitalized population: the role of age. Journal of cardiac failure. 2012;18(8):645-53.
13. Azad N, Lemay G. Management of chronic heart failure in the older population. Journal of geriatric cardiology: JGC. 2014;11(4):329.
14. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003;107(2):223-5.
15. Mitchell JE. Emerging role of anemia in heart failure. The American journal of cardiology. 2007;99(6):S15-S20.
16. Anker SD, Sharma R. The syndrome of cardiac cachexia. International journal of cardiology. 2002;85(1):51-66.
17. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? American heart journal. 2004;147(5):924-30.
18. Means Jr RT. Advances in the anemia of chronic disease. International journal of hematology. 1999;70(1):7-12.
19. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, et al. Etiology of anemia in patients with advanced heart failure. Journal of the American College of Cardiology. 2006;48(12):2485-9.
20. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. European heart journal. 2007;28(2):166-71.
21. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. The Journal of clinical investigation. 1997;100(9):2310-4.
22. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. Journal of the American College of Cardiology. 2005;45(3):391-9.
23. van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, et al. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation. 2005;112(12):1743-7.
24. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation. 2000;102(25):3060-7.
25. Androne A-S, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107(2):226-9.
26. McCullough PA, Lepor NE. Anemia: a modifiable risk factor for heart disease. Reviews in Cardiovascular Medicine. 2005;6(S3):1-3.
27. Anand IS. Pathogenesis of anemia in cardiorenal disease. Reviews in Cardiovascular Medicine. 2005;6(S3):13-21.
28. Olivetti G, Lagrasta C, Quaini F, Ricci R, Moccia G, Capasso JM, et al. Capillary growth in anemia-induced ventricular wall remodeling in the rat heart. Circulation research. 1989;65(5):1182-92.
29. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. American Journal of Kidney

Diseases. 1999;34(1):125-34.
30. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. Journal of the American Society of Nephrology. 2000;11(5):912-6.
31. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. Journal of the American Society of Nephrology. 2005;16(7):2180-9.
32. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne A-S. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003;107(2):294-9.
33. Berry C, Norrie J, Hogg K, Brett M, Stevenson K, McMurray JJ. The prevalence, nature, and importance of hematologic abnormalities in heart failure. American heart journal. 2006;151(6):1313-21.
34. Rich MW, McSherry F, Williford WO, Yusuf S, Group DI. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. Journal of the American College of Cardiology. 2001;38(3):806-13.
35. Balducci L. Epidemiology of anemia in the elderly: information on diagnostic evaluation. Journal of the American Geriatrics Society. 2003;51(3s):2-9.

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